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HEALTH AFFAIRS

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MEMORANDUM FOR DEPUTY SURGEON GENERAL OF THE ARMY
DEPUTY SURGEON GENERAL OF THE NAVY
DEPUTY SURGEON GENERAL OF THE AIR FORCE

SUBJECT: Establishment of Case Management Guidelines for Smallpox Vaccine Associated Myopericarditis

REFERENCES:

1. Deputy Secretary of Defense Memorandum, "Smallpox Vaccination Program," September 30, 2002
2. Under Secretary of Defense for Personnel and Readiness Memorandum, "Policy on Administrative Issues Related to Smallpox Vaccination Program (SVP)," December 13, 2002
3. Assistant Secretary of Defense for Health Affairs Memorandum, "Clinical Policy for the DoD Smallpox Vaccination Program (SVP)," November 26, 2002

Myopericarditis has historically been associated with vaccination for smallpox (vaccinia virus). Until recently, it has been a rare or unrecognized event after vaccination with the currently utilized strain of vaccinia virus (New York City Board of Health; Dryvax®, Wyeth Laboratories, Marietta, PA). Ongoing evaluation of health outcomes among Armed Forces personnel indicates individuals vaccinated for smallpox are at higher risk for myopericarditis than those not vaccinated. Ongoing review of cases diagnosed to date indicate a need to standardize evaluation and clinical management to decrease variation and provide ready access to clinical consultative services, assure access to care for longer-term follow-up for individuals separating from active duty, reserve component and National Guard personnel, and a need to document outcomes for future smallpox vaccine program management.

This memorandum provides a uniform approach for evaluation and establishes a program for consultation and long-term follow-up of individuals diagnosed with smallpox vaccine associated myopericarditis. A tri-service team supporting the DoD Vaccine Healthcare Center (VHC) Network developed the attached guidelines for clinicians. Forward deployed medical support units should be aware of and use the guidelines for the diagnosis and treatment of myopericarditis associated with smallpox vaccination. The guidelines will be modified in an iterative process as new information and clinical experience evolve, and will be available at www.vaccines.mil. To support clinicians seeking multi-disciplinary consultation, the Military Vaccine (MILVAX) Agency established a 24/7 toll-free bridge number for short-notice teleconferencing. Clinicians wishing to consult via this teleconference bridge with VHC staff and/or military cardiologists regarding optimal care should call the DoD Vaccine Clinical Call

Center at (866) 210-6469. Additional consultative support is available via e-mail at ASkVHC@amedd.army.mil.

All DoD beneficiaries, including Reserve component personnel who received their smallpox vaccine while in a duty status, with a clinically verified diagnosis of post-smallpox vaccine myopericarditis will be enrolled in the central registry maintained by the VHC Network and be followed using the attached clinical guidelines for a minimum of 12 months from the date of initial diagnosis. The Vaccine Adverse Event Reporting System (VAERS) should be used according to service policy. Patient informed consent is not required as part of enrollment. Enrollment in this registry will facilitate long-term clinical follow-up, delivery of appropriate clinical care, and a greater understanding of potential sequelae of this clinical manifestation. Upon enrollment VHC staff should help ensure appropriate 6 and 12-month follow-up in coordination with the patient's case manager.

Those individuals requiring medical treatment/evaluation should be retained on Active Duty pending resolution of the medical condition or completion of the disability evaluation. Each Service will coordinate with the Military Medical Support Office (1-888-MHS-MMSO), as needed, to provide appropriate civilian medical follow-up and payment arrangements for Reserve Component personnel.

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Clinical and Program Policy

Attachment:
As stated

Pericarditis-Myocarditis-Cardiac Evaluation Tables, Suitable for Evaluation After SmallpoxVaccination

DoD Vaccine Healthcare Centers (VHC), **Version: 5/30/2003 8:38 AM**

Smallpox vaccine(s) administered In Past 30 Days

Possible clinical symptoms: chest pain, shortness of breath, palpitations, unexplained syncope, dry cough

Initial Evaluation (Case Definition CDC MMWR May 30, 2003 / 52(21);492-496)

History: characterize symptoms [1]
Detailed vaccination history & dates
• especially smallpox or other live vaccines
Past medical history: Cardiac risk factors [2]

Physical examination [3]
Chest X-ray: PA/Lateral
Electrocardiogram (ECG) [4]
Laboratory: Troponin, CK-MB
Echocardiogram

SAVE Plasma, Buffy Coat, Serum (stored blood protocol)

A. Symptoms Only <-> **B. Symptoms + abnormality of cardiac enzymes, ECG, echocardiogram** <-> **C. Progressive symptoms, LVEF < 40-45%, CK > 1,000, ventricular dysrhythmias, hemodynamic instability**

A. Evaluate, treat, consult as indicated
- Evaluate as soon as possible
- Document normal ECG, troponin, CK, CRP, other if indicated
- Reclassify if any abnormality or indicated by expert review
- Enter in VHC registry for FU monitoring as suspect case if symptoms continue
- Consider non-cardiac etiology
- Monitor if continued symptoms
- Treat symptomatically[10]

Approach to new severe &/or persistent complaints
- Evaluate & treat with consultation as needed
- New problem, vaccine temporal association, serious impact on quality of life, unremitting: Contact VHC via 866-210-6469

B. Cardiology evaluation, treat, consult as indicated
- Work up & treat for acute coronary syndrome[7]
- Differential of myo-pericarditis [6]
- **Contact VHC + Cardiology**

Special studies[5]
- Serial daily enzymes for 5 days or normalization, and at 3 weeks
- Viral work-up (serology, PCR)
- Establish functional impairment

Therapeutic options: NSAID, acetaminophen, COX2 inhibitor, other Rx such as steroids?

Management & Recovery[10-12]
- Profile (limited duty) for 4-6 weeks with care plan
- Follow-up at 6 & 12 weeks and 6 & 12 months with repeat ECG, echocardiogram, enzymes, and exercise test, for clearance at home duty station

C. Cardiology evaluation, treat, consult as indicated
- Promptly work up & treat for acute coronary syndrome, as indicated[7]
- Differential of myo-pericarditis [6]
- **Contact VHC + Cardiology**
- Viral work-up (serology, PCR)

Transfer to Tertiary Care Center: consider limitations of facility
- Apply elements outlined in **B**

Individual case management
- **Monitor & document recovery**
- VHC case management with tracking at 4-6 months and 12 month evaluation by cardiology

A-C Refer to VHC Network for second level review (CISA/CDC/VHC): Echocardiograms, ECGs, cardiac isoenzyme results, copy of records and patient and provider contact information. **Key VHC Consultant Sites**: Brooke & Walter Reed AMC

Consultation. Clinicians wishing to consult with Vaccine Healthcare Center and/or military cardiologists regarding optimal care should call the DoD Vaccine Clinical Call Center at 866-210-6469, to request a clinical cardiovascular consult. **NOTE**: Footnotes and additional information described on accompanying sheets.

Recommended Pericarditis-Myocarditis-Cardiac Evaluation Guidelines Suitable for Evaluation Post-Smallpox Vaccination

DoD Vaccine Healthcare Centers (VHC), 30 May 2003

Footnote #	Topic	Documentation Categories	Documentation Details, Comments
1	Chest pain type	Category of patient's chest pain type if present (choose one): I. Atypical chest pain: Pain, pressure, or discomfort in the chest, neck, or arms not clearly exertional or not otherwise consistent with pain or discomfort of myocardial ischemic origin II. Stable chest pain: Chest pain without a change in frequency or pattern for the 2 weeks before this procedure. Chest pain is controlled by rest and/or sublingual/oral/transcutaneous medications. III. Unstable chest pain: Chest pain that occurred at rest and was prolonged, usually lasting more than 20 minutes. Recent acceleration of chest pain reflected by an increase in severity	
	Number of episodes of chest pain in last 72 hours	Number of distinct episodes of chest pain that occurred in the last 72 hours before evaluation	
	Secondary cause of chest pain (yes/no)	Note whether the chest pain was precipitated by a secondary factor such as known atherosclerotic coronary artery disease, fever, anemia, hypoxemia, tachycardia, thyrotoxicosis, or severe valvular disease	
	Reproducibility of symptoms	Note whether the chest pain is reproducible by either deep respiration (pleuritic), positional changes or pressure sensitive	
	Heart failure	Patient with complaint of dyspnea on exertion, resting shortness of breath, paroxysmal nocturnal dyspnea, orthopnea, edema, weight gain	
	Dysrhythmia	Patient with complaint of palpitations, rapid or slow heart rate. Documentation of concominant symptoms of syncope (duration), dizziness or light headedness associated with symptoms	
2	Prior angina	History of angina before the current admission. "Angina" refers to evidence or knowledge of symptoms before this acute event described as chest pain or pressure, jaw pain, arm pain, or other equivalent discomfort suggestive of cardiac ischemia. Indicate if angina existed more than 2 weeks before admission and/or within 2 weeks before admission.	
	Previous myocardial infarction (MI)	The patient has had at least 1 documented previous MI before admission.	
	Prior congestive heart failure (CHF)	History of CHF. "CHF" refers to evidence or knowledge of symptoms before this acute event described as dyspnea, fluid retention, or low cardiac output secondary to cardiac dysfunction, or the description of rales, jugular venous distension, or pulmonary edema before the current admission.	
	Previous percutaneous coronary intervention (PCI)	Previous PCI of any type (balloon angioplasty, atherectomy, stent, or other) done before the current admission. Date should be noted.	
	Previous coronary artery bypass graft (CABG)	Previous CABG done before the current admission. Date should be noted.	
	Prior catheterization with stenosis greater than or equal to 50%	Documented coronary artery disease (CAD) at coronary angiography at any time before the current admission, with at least a 50% stenosis in a major coronary artery. If the patient had a cardiac catheterization before the index event that demonstrated a stenosis of 90% and that was successfully stented to a 0% residual, this should be coded as "yes," because a stenosis of greater than or equal to 50% was documented.	
	History of stroke	Documented history of stroke or cerebrovascular accident (CVA). Typically, a patient has had a history of stroke if there was loss of neurological function caused by an ischemic event with residual symptoms at least 24 hours after onset. The year of the most recent stroke before the current admission should be noted.	
	History of transient ischemic attack (TIA)	A focal neurological deficit (usually corresponding to the territory of a single vessel) that resolves spontaneously without evidence of residual symptoms at 24 hours	
	Peripheral arterial disease	Peripheral arterial disease can include the following: 1. Claudication, either with exertion or at rest 2. Amputation for arterial vascular insufficiency 3. Vascular reconstruction, bypass surgery, or percutaneous intervention to the extremities 4. Documented aortic aneurysm 5. Positive noninvasive test (e.g., ankle brachial index less than 0.8)	

	Diabetes	History of diabetes, regardless of duration of disease, need for antidiabetic agents, or a fasting blood sugar greater than 7 mmol/l or 126 mg/dl. If yes, the type of diabetic control should be noted (check all that apply): 1. None 2. Diet: Diet treatment 3. Oral: Oral agent treatment 4. Insulin: Insulin treatment (includes any combination of insulin)
	Hypertension	Hypertension as documented by: 1. History of hypertension diagnosed and treated with medication, diet, and/or exercise 2. Blood pressure greater than 140 mmHg systolic or 90 mmHg diastolic on at least 2 occasions 3. Current use of antihypertensive pharmacological therapy
	Smoking	History confirming cigarette smoking in the past. Choose from the following categories: 1. Current: Smoking cigarettes within 1 month of this admission 2. Recent: Stopped smoking cigarettes between 1 month and 1 year before this admission 3. Former: Stopped smoking cigarettes greater than 1 year before this admission 4. Never: Never smoked cigarettes
	Dyslipidemia	History of dyslipidemia diagnosed and/or treated by a physician. National Cholesterol Education Program criteria include documentation of the following: 1. Total cholesterol greater than 200 mg/dl (5.18 mmol/l); or 2. Low-density lipoprotein (LDL) greater than or equal to 130 mg/dl (3.37 mmol/l); or 3. High-density lipoprotein (HDL) less than 40 mg/dl (1.04 mmol/l). Treatment is also initiated if LDL is greater than 100 mg/dl (2.59 mmol/l) in patients with known coronary artery disease, and this *would* qualify as hypercholesterolemia.
	Family history of CAD	Any direct blood relatives (parents, siblings, children) who have had any of the following at age less than 55 years: 1. Angina 2. MI 3. Sudden cardiac death without obvious cause
	Lung disease	Documented history of chronic lung disease (i.e., chronic obstructive pulmonary disease) or currently being treated with pharmacological therapy (e.g., inhalers, theophylline, aminophylline, or steroids) and/or has a forced expiratory volume in 1 second (FEV1) less than 75%, room air pO2 less than 60%, or room air pCO2 greater than 50%. Acute lung injury to include pulmonary embolism/deep vein thrombophlebitis.
	Gastrointestinal disease	Documented history of either gastroesophageal reflux disease, esophagitis, peptic ulcer disease, or currently being treated with pharmacologic therapy (e.g. H_2-antagonists (cimtedine, ranitidine, etc.), or proton pump inhibitors (omeprazole, lansoprazole, etc.)). History of pancreatitis or cholelithiasis or other gallbladder disease.
	Prior vaccination history and adverse events	Note made of all vaccinations received within 30 days of presentation, to include location of immunization. Note made of prior adverse reactions with vaccinations to include, but not limited to, arthralgias, myalgias, headache, shortness of breath, chest pain, febrile illness
3	Gender	Patient's gender: male or female
	Date of birth	Day, month, and year of the patient's birth
	Race	Patient's race: 1. White 2. Black 3. Hispanic 4. Asian 5. Native American 6. Other race not listed (Note: These categories could be used in a "check all that apply" format to identify mixed races.)
	Heart rate	Heart rate (beats per minute) should be the recording that was done closest to the time of presentation to the healthcare facility
	Systolic and diastolic blood pressure (at time of presentation	Supine systolic and diastolic blood pressure (mmHg) should be the recording that was done closest to the time of presentation to the healthcare facility and on

	and on discharge)	discharge
	Respiratory rate	Respiratory rate (breaths per minute)
	Temperature	Temperature (in Fahrenheit or Celsius) with indication as to method taken, either aural, oral, rectal, or non-invasive (skin probe). Should be the recording that was done closest to the time of presentation to the healthcare facility
	Height	Patient's height in centimeters or inches
	Weight	Patient's weight in kilograms or pounds
	Vaccination site	Vaccination site healing?
	Cardiac exam	Heart rate regular/irregular, absence/presence of S4, S3 Absence/presence of murmur or rub Point of maximal impulse (PMI, apex) lateral
	Jugular venous pressure	Normal/elevated
	Lung exam	Rales, wheezes, etc. None (absence of rales over the lung fields) Mild CHF (rales over 50% or less of the lung fields). Evidence of new pulmonary vascular congestion on chest radiograph also meets the definition. Severe CHF (rales over more than 50% of the lung fields). Evidence of pulmonary edema on chest radiograph would also meet this definition.
	Extremities	Edema on peripheral extremities, with notation as to evidence of sustained depression (pitting), and amount of depression (in millimeters, or 1-4+ scale)
	Lymphatics	Adenopathy with documentation of location (ancillary, clavicular, submental, cervical, inguinal)
4	First 12-lead ECG: date and time	Note date and time the first 12-lead ECG was performed for acute episode (whether in a prehospital setting, emergency department, or inpatient unit).
	Location of ECG changes	The location of each type of ECG change listed below can be broken into 4 categories: 1. Inferior leads: II, III, aVF 2. Anterior leads: V1 to V4 3. Lateral leads: I, aVL, V5 to V6 4. Diffuse leads: use if similar type of ECG changes identified in ≥9 of 12 leads.
	Type of ECG changes	1. ST-segment elevation indicates greater than or equal to 1 mm (0.1 mV) elevation in 2 or more contiguous leads 2. ST-segment depression of at least 0.5 mm (0.05 mV) in 2 or more contiguous leads (includes reciprocal changes) 3. T-wave inversion of at least 1 mm (0.1 mV) including inverted T waves that are not indicative of acute MI 4. Q waves refer to the presence of Q waves that are greater than or equal to 0.03 seconds in width and greater than or equal to 1 mm (0.1 mV) in depth in at least 2 contiguous leads
	Bundle-branch block (BBB) and type	The presence of left or right BBB should be noted, as well as whether it is new, old, or of uncertain timing
	Rhythm	The categories of rhythm are as follows: 1. Sinus rhythm 2. Atrial fibrillation (or flutter) 3. Paced 4. Other rhythm (e.g., ventricular tachycardia, supraventricular tachycardia)
	Conduction abnormality	1.Conduction abnormalities including: Ventricular tachycardia 2. Supraventricular tachycardia 3. Sinus arrhythmia 4. Premature beats to include premature ventricular complexes (PVC), premature supraventricular/atrial complexes (PACs).

5			
	Complete blood count	The presentation CBC, to include differential, with emphasis on eosinophil and lymphocyte count should be noted. The upper limit of normal of WBC, Hgb, Plt, and differential as determined by individual hospital laboratory standards should be reported.	
	Cardiac enzymes		
	All values	All CK, CK-MB, and troponin values during the evaluation should be noted; include the units, date, and time. The upper limit of normal of CK-MB as defined by individual hospital laboratory standards should be noted. For troponin values, indicate which type: T or I.	
	B-type natriuretic peptide		
	All values	All BNP values during the hospitalization should be noted; include units, date, and time	
	Inflammatory markers		
	All values	All erythrocyte sedimentation rate and C-reactive protein values during the evaluation should be noted; include units, date, and time. Report the upper limit of normal as defined by individual hospital laboratory standards.	
	Immune complex screening		
	All values	All C3, C4, CH50, Raji cell, C1q assay values during the evaluation should be noted; include units, date, and time. Report the upper limit of normal as defined by individual hospital laboratory standards.	
	Cultures: Viral		
	All values	All viral cultures (nasal wash, urine, feces) for adenovirus, influenza viruses or enteroviruses should be noted to include date and time. Results of cerebrospinal fluid viral cultures including shell vial culture that looks specifically for enteroviruses, herpes simplex viruses, and cytomegalovirus should be noted to include date and time.	
	Serologies: Viral		
	All values	All enterovirus, influenza, coxsackie B, Lyme, hepatitis B IgM and core IgG values and titers during the evaluation should be noted; include units, date, and time to differentiate between acute and convalescent sera.	
	Collagen vascular screening		
	All values	All ANA, Anti-DS DNA, ENA, etc. values during the evaluation should be noted; include units, date, and time. Report the patterns associated with positive assays.	
	Other labs		
	Total serum cholesterol level	The first total serum cholesterol level and type of units should be noted	
	LDL	First serum low density lipoprotein (LDL) and units (either calculated or direct, if measured)	
	HDL	First serum high density lipoprotein (HDL) level and units	
		First serum C-reactive protein level and units	
	Serum creatinine	First creatinine level and units	
	Hemoglobin A1c	Documented laboratory value and units for patient's hemoglobin A1c	
6	Pericarditis, myocarditis Case definition items (Case Definition CDC MMWR May 30, 2003 / 52(21);492-496)	Elevated cardiac enzymes	↑ Troponin, CK-MB, and/or CK
		Electrocardiogram (ECG) abnormalities	ECG: No evolution to Q waves
		Physical findings	Rub, S3
		Chest x-ray	Heart failure signs
		Echocardiogram abnormalities	Pericardial effusion, ↓ left-ventricular (LV) function
		±Magnetic resonance imaging (MRI) with gadolinium ±^{111}In-Cardiac scanning	Pericardial versus myocardial uptake

		±Endomyocardial biopsy (exclude active vaccinia by PCR before recommending steroids) ±Viral diagnostics	Characteristic histology
7	Stress test	Indicate whether an exercise tolerance or pharmacological stress test was performed during the hospital stay. Date should be noted. Indicate if the test involved ECG alone, or either radionuclide, imaging or echocardiogram.	
	Ischemia result (positive, negative, equivocal)	Positive: On an exercise tolerance test, the patient developed either: a. Both ischemic discomfort and ST shift greater than or equal to 1 mm (0.1 mV) (horizontal or downsloping) or b. New ST shift greater than or equal to 2 mm (0.2 mV) (horizontal or downsloping) believed to represent ischemia even in the absence of ischemic discomfort If the patient had an equivalent type of exercise test (e.g., exercise thallium or MIBI test, stress echocardiography, or dipyridamole, thallium, or adenosine radioisotope scan) that showed definite evidence of ischemia (e.g., an area of clear reversible ischemia), this should be considered a positive test. 2. Negative: No evidence of ischemia (i.e., no typical angina pain and no ST shifts). 3. Equivocal: Either: a. Typical ischemic pain but no ST shift greater than or equal to 1 mm (0.1 mV) (horizontal or downsloping) or b. ST shift of 1 mm (0.1 mV) (horizontal or downsloping) but no ischemic discomfort c Imaging testing Note presence or absence of a fixed defect indicating an old MI	
	Ejection fraction (EF)	The first EF obtained during the hospital stay. It is the percent of blood emptied from the ventricle at the end of contraction and can be obtained, in preferred order, from a left ventriculogram, radionuclide ventriculography, or echocardiogram. If only a range is estimated for EF, the midpoint of the range should be the value noted. Note type of test used for EF: contrast ventriculography, radionuclide ventriculography or echocardiography. Note also whether it was estimated or calculated.	
	Cardiac catheterization	Diagnostic cardiac catheterization/angiography performed during the hospital stay. Date should be noted. Note percentage occlusion, from 0 to 100%, associated with the identified vessel systems. In instances where multiple lesions are present, enter the highest percentage stenosis noted. The systems of interest are as follows and should include major branch vessels of greater than 2 mm diameter: LAD or any major branch vessel, LCx or any major branch vessel, RCA or any major branch vessel, left main, bypass grafts	
8	Other special studies	Auto-antibodies for myocardium Special studies on biopsy	To be developed
9	Normal tests but persistent symptoms	If symptoms persist > 3 months, consider further evaluation with specialty referrals, VHC referral.	To be developed
10	Therapeutic options • Mild to moderate	Aspirin or non-steroidal anti-inflammatory therapy	To be developed
11	Therapeutic options • Symptoms, normal LV function, evidence of inflammation	Corticosteroids?	To be developed
12	Therapeutic options • Symptoms, abnormal LV function (e.g., LV ejection fraction, LVEF) • Evidence of inflammation? • Progressive disease	Corticosteroids? Vaccinia Immune Globulin?	To be developed

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